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October 13, 2005

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Docket Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

Re: The American Heart Association's Comments on File Code 205P-0048 : PROFESSIONAL LABELING FOR ASPIRIN DOSING IN ORDER FOR SECONDARY CARDIOVASCULAR PREVENTION.

Dear FDA:

On behalf of the American Heart Association, its division the American Stroke Association, and its 22.5 million volunteers and supporters, we submit the following comments relative to the use of aspirin in primary and secondary prevention of events related to atherosclerotic vascular disease. The American Heart Association is dedicated to improving the quality of care available to patients suffering from or at risk for heart disease, stroke or other cardiovascular diseases. Heart disease is the nation's leading cause of death. Stroke is the number three killer. Both are leading causes of significant, long-term disability. Over 70 million Americans -- almost 1 in 4 -- suffer from some form of cardiovascular disease. It is expected that heart disease, stroke and other cardiovascular diseases will cost the nation $93.5 billion in 2005, including $241.9 million in direct medical costs.

Toward this end the American Heart Association has promoted better understanding of the most effective approaches to primary and secondary prevention of events due to atherosclerotic cardiovascular disease. The use of aspirin for secondary prevention of atherosclerotic cardiovascular events is well-documented and the association recommends its use in a range of doses as supported by our guidelines (1-5). The association has also issued guidelines for the primary prevention of cardiovascular disease and stroke (6). This statement emphasizes the importance of preventing the first episode of coronary heart disease, stroke, or peripheral vascular disease. Aspirin is specifically cited as one of the preventive strategies, and low dose aspirin is recommended for those individuals at higher risk for coronary heart disease (especially for those with a 10 year risk of $\geq$ 10%). This is consistent with the recommendations from the U.S. Preventive Services Task Force (USPSTF) (7), although slightly more conservative. A meta-analysis of five published randomized trials of aspirin in the primary prevention of cardiovascular disease, released in 2003, supported the use of aspirin for primary prevention of myocardial infarction (MI) (8). Additionally, in 2004, the association issued evidence-based guidelines for cardiovascular disease prevention that were specific to women (9). In these guidelines low-dose aspirin is recommended for all women in the high risk category (10 year risk>20%) and low-dose aspirin should be considered in intermediate risk women (10 year risk 10% to 20%).

A recently published randomized trial of low-dose aspirin for primary prevention of CV disease in women (10) showed that the effect of aspirin may differ based on the vascular outcome and age. Overall, the 10-year risk of CHD events in this cohort was <10% indicating that these women were at lower risk. Despite the lack of benefit in the primary, combined endpoint of MI, stroke, or death, aspirin significantly reduced the risk of stroke events, particularly ischemic stroke. However, aspirin significantly lowered the risk of MI and

particularly ischemic stroke. However, aspirin significantly lowered the risk of MI and ischemic stroke in the subgroup of women 65 years of age and older. Thus, with regard to the prevention of MI, aspirin may not have the same effects in women younger than 65 as in older women and in men. These data suggest that the use of aspirin for primary prevention of MI in lower risk women younger than 65 deserves further investigation. Higher risk women and those over age 65, among whom the majority of MIs and strokes are observed, are likely to benefit from aspirin.

Aspirin is not without adverse risks. Low dose aspirin increases the risk of gastrointestinal bleeding as well as hemorrhagic stroke. The data, which were summarized by the USPSTF (11) show that the risk-benefit ratio is most favorable in those patients at higher risk. The American Heart Association defines this group as a 10-year risk $\geq$ 10%. The net benefit of aspirin increases with increasing cardiovascular risk. We are concerned that low risk individuals may misinterpret the risk-benefit ratio and therefore be unnecessarily exposed to the adverse risks of aspirin. Currently there is no professional labeling of aspirin for primary prevention of MI, stroke, or any other atherosclerotic vascular event. If labeling is changed to include its recommended use for primary prevention of MI, stroke and/or other CV events, it is critical to clarify to the public which individuals may benefit from its use, including its use in women under the age of 65.

Both the AHA and the USPSTF recommendations categorize patients according to their global risk for coronary heart disease. However, neither patients nor many healthcare providers will be familiar with how to calculate this global risk. We believe that an educational effort should be mounted, and tools should be widely available, for the public and for healthcare professionals for calculation of this global risk to better select the intermediate and high-risk groups for treatment with aspirin.

In summary, we conclude that the available evidence supports a role for aspirin in both primary and secondary prevention of atherosclerotic vascular events including MI and stroke in defined at-risk populations. The association recommends low-dose aspirin in a range of doses depending on the vascular condition. However, we also believe that it will be critical to find means to avoid adverse risks caused by aspirin in those individuals at low risk for atherosclerotic vascular disease. We recommend that individuals considering use of low dose aspirin should first check with their physician.

If you need any additional information, please don't hesitate to contact Kathryn Taubert, PhD, Senior Scientist, at 214-706-1455 or ktaubert@heart.org.

Sincerely,

Robert H. Eckel, MD, FAHA
President

Cc: Kathryn Taubert, PhD, FAHA
Rose Marie Robertson, MD, FAHA
Walter Ellenberg, PhD
Meg Pease-Fye, MS

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